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16. ABSTRACT

To assess the relative safety of chronically administered chlorine water disinfectants in man, a controlled study was undertaken. The clinical evaluation was conducted in the three phases common to investigational drug studies. Phase I, a rising does tolerance investigation, examined the acute effects of progressively increasing single doses of chlorine disinfectants to normal healthy adults male volunteers. Phase II considered the impact on normal subjects of daily ingestion of the disinfectants at a concentration of 5mg/l. for twelve consecutive weeks. Persons with a low level of glucose-6-phosphate dehydrogenase may be expected to be especially susceptible to oxidative stress; therefore, in Phase III, chlorite at a concentration of 5mg/l. was administered daily for twelve consecutive weeks to a small group of potentially at-risk glucose-6-phosphate dehydrogenase-deficient subjects. Physiological impact was assessed by evaluation of a battery of qualitative and quantitative tests. The three phases of this controlled double-blind clinical evaluation of chlorine dioxide and its potential metabolites in human male volunteer subjects were completed uneventfully. There were no obvious undesirable clinical sequellae noted by any of the participating subjects or by the observing medical team. In several cases, statistically significant trends in certain biochemical or physiological parameters were associated with treatment; however, none of these trends was judged to have physiological consequence. One cannot rule out the possibility that, over a longer treatment period, these trends might indeed achieve proportions of clinical importance.

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Controlled Clinical Evaluations of Chlorine Dioxide, Chlorite and Chlorate in Man

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To assess the relative safety of chronically administered chlorine water disinfectants in man, a controlled study was undertaken. The clinical evaluation was conducted in the three phases common to investigational drug studies. Phase I, a rising does tolerance investigation, examined the acute effects of progressively increasing single doses of chlorine disinfectants to normal healthy adult male volunteers. Phase II considered the impact on normal subjects of daily ingestion of the disinfectants at a concentration of 5 mg/l. for twelve consecutive weeks. Persons with a low level of glucose-6-phosphate dehydrogenase may be expected to be especially susceptible to oxidative stress; therefore, in Phase III, chlorite at a concentration of 5 mg/l. was administered daily for twelve consecutive weeks to a small group of potentially at-risk glucose-6-phosphate dehydrogenase-deficient subjects. Physiological impact was assessed by evaluation of a battery of qualitative and quantitative tests. The three phases of this controlled double-blind clinical evaluation of chlorine dioxide and its potential metabolites in human male volunteer subjects were completed uneventfully. There were no obvious undesirable clinical sequellae noted by any of the participating subjects or by the observing medical team. In several cases, statistically significant trends in certain biochemical or physiological parameters were associated with treatment; however, none of these trends was judged to have physiological consequence. One cannot rule out the possibility that, over a longer treatment period, these trends might indeed achieve proportions of clinical importance. However, by the absence of detrimental physiological responses within the limits of the study, the relative safety of oral ingestion of chlorine dioxide and its metabolites, chlorite and chlorate, was demonstrated.

Introduction

Chlorine dioxide is currently under serious consideration in the United States as an alternative to chlorine water treatment. Before chlorine dioxide may be used routinely as a water disinfectant, the safety of oral human ingestion of chlorine dioxide and its by-products must be assessed. For this purpose, a controlled clinical evaluation of chlorine dioxide, chlorite and chlorate was undertaken under the auspices of USEPA HERL #CR805643.

The study was conducted in three parts. Phase I was designed to evaluate the acute physiological effects of progressively increasing doses of disinfectants administered to normal healthy adult males. Chronic ingestion by normal male volunteers was studied in Phase II. Phase III assessed the physiological response of a small group of potentially susceptible individuals, those deficient in glucose-6-phosphate dehydrogenase, to chronic ingestion of chlorite.

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Methods

Subject Selection

For Phase I and for Phase II, normal healthy adult male volunteers were selected. No prospective study participant who exhibited a significant abnormality in the routine clinical serum analysis,

blood count, urinalysis, or electrocardiogram was selected. Subjects manifested no physical abnormalities at the pretreatment examination, were 21 to 35 years of age, and weighed within ± 10% of normal body weight for their frame and stature. A history of disease or any medical or surgical condition which might interfere with the absorption, excretion, or metabolism of substances by the body precluded inclusion. Regular drug intake prior to the start of the investigation, either therapeutic or recreational, resulted in exclusion from the study. Normal methemoglobin levels, thyroid function, and glutathione levels were mandatory. Written informed consent was obtained from each subject prior to initiation of treatment.

For Phase III, volunteers were defined as glucose-6-phosphate dehydrogenase (G-6-PD)-deficient on the basis of a hemoglobin G-6-PD level of less than 5.0 IU/GM hemoglobin in the pre-study screening. Phase III subjects were normal in all other respects.

Water Disinfectant Preparation

A detailed description of the water disinfectant preparation techniques has been presented by Lubbers and Bianchine (*1*). In general, freshly prepared stock solutions of chlorine dioxide, sodium chlorite, sodium chlorate, chlorine and chloramine were assayed by the colorimetric techniques of Palin (*2*) then diluted with organic-free demineralized deionized water to appropriate concentrations. Individual bottles were capped and stored in the dark under refrigeration until use. All bottles were coded by an independent observer and the identity of each bottle remained "double-blind" to both the investigative staff and the volunteer subjects.

Study Design: Phase I

The 60 volunteers in Phase I were divided at random into six treatment groups (*1*). Ten persons were assigned to receive each of the disinfectants; the ten members of the control group received untreated water. The study involved a series of six sequences of three days each. Treatment concentrations were increased for each treatment. The specific concentrations or disinfectant administered to the study participants are listed in Table 1. A clinical evaluation of the collection of blood and urine samples for determination of pretreatment baseline laboratory values preceded the first treatment. On the first day of each three day treatment sequence, each volunteer ingested 1000 ml of the water in two portions. The second 500 ml portion aliquot was administered 4 hr after the first. Each 500 ml portion was consumed within 15 min. Only two doses of disinfectant were administered on the first day of each treatment sequence. No disinfectant was administered on the second and third day of each sequence, since these two days were to serve as followup observation days. The second day of the treatment sequence consisted of a physical examination and collection of blood and urine samples for determination of posttreatment laboratory values. On the third day, each volunteer was given a physical examination to determine residual effects of treatment with the water disinfectants and byproducts.

Taste evaluations were obtained at each dose level. Study participants were asked to rate the treated water as very unpleasant, slightly unpleasant, not pleasant, pleasant, or tasteless.

Study Design: Phase II

The sixty volunteers of Phase II were divided at random into six treatment groups of ten subjects each (*3*). In order to assure efficient management of the 60 subjects, they were randomly assigned to three subsets. These subsets were sequentially entered into the study on three successive days and exited from this study in a similar fashion. For all of the treatment groups, the concentration of disinfectants ingested was 5 mg/l. The control group received untreated water. Each subject received 500 ml daily for 12 weeks. Physicals, collection of blood and urine samples for laboratory assays, and taste evaluations were conducted on a weekly basis during the treatment period and for 8 weeks following cessation of treatment.

Study Design: Phase III

The three glucose-6-phosphate dehydrogenase-deficient subjects of Phase III were given sodium chlorite at a concentration of 5 mg/l. chlorite (4). The treatment protocol was identical to that of Phase II, with daily administration of 500 ml of solution to each volunteer.

Evaluation Procedures

An extensive battery of parameters was monitored to assess the biochemical and physiological response to the oral ingestion of the water disinfectants and water treatment by-products (Table 2). All laboratory determinations of biochemical parameters were conducted by a licensed medical laboratory, Consolidated Biomedical Laboratories, Inc. (CBL), Columbus, Ohio, HEW license number 34–1030. For each volunteer, pretreatment baseline values and six sets of posttreatment values were compiled. Laboratory tests were carefully chosen.

Table 1. Concentration of disinfectants in phase I: acute rising dose tolerance.[a]

Water disinfectant	Disinfectant concentration, mg/l.					
	Day 1	Day 4	Day 7	Day 10	Day 13	Day 16
Chlorate	0.01	0.1	0.5	1.0	1.8	2.4
Water control	0	0	0	0	0	0
Chlorine dioxide	0.1	1.0	5.0	10.0	18.0	24.0
Chlorite	0.01	0.1	0.5	1.0	1.8	2.4
Chlorine	0.1	1.0	5.0	10.0	18.0	24.0
Chloramine	0.01	1.0	8.0	18.0	24.0	

[a]For each dose, two portions of 500 ml each were administered at 4-hr intervals.

Table 2. Biochemical parameters assayed in the controlled clinical evaluation of chlorine dioxide, chlorite and chlorate in man.

Serum chemistry	Plasma glucose, sodium, potassium, chloride, urea nitrogen, creatinine, BUN/creatinine ratio, uric acid, calcium, phosphorus, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, lactic dehydrogenase, cholesterol, triglycerides, total protein albumin, globulin, albumin/globulin ratio, iron
Blood count	Platelet count, white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, high peroxidase activity, neutrophils, lymphocytes, monocytes, eosinophils, basophils, large unstained cells
Urinalysis	Color,[a] appearance,[a] specific gravity, pH, protein, sugar,[a] acetone, blood,[a] white blood count, red blood count, casts,[a] crystals,[a] bacteria,[a] mucus[a], amorphous cells,[a] epithelial cells
Special tests	Serum haptoglobin, sickle cell,[a] methemoglobin, glucose-6-phosphate dehydrogenase, Coombs test,[a] hemoglobin electrophoresis,[a] T-3 (uptake), T-4 (RIA), free thyroxine index, electrocardiogram[a]
Physical exam	Systolic blood pressure, diastolic blood pressure, respiration rate, pulse rate, oral temperature

[a]These parameters yielded qualitative data only; no statistical analysis was performed.

On the basis of the literature (*5–8*), areas of suspected biochemical response to ingestion of chlorine oxidants were defined; a portion of the test battery was specifically devoted to monitoring this response. Red blood cell surface antibody formation was clinically monitored by the qualitative Coombs test; thyroid function by T-3 (uptake), T-4 (RIA), and free thyroxine; and response to oxidative stress by glucose-6-phosphate dehydrogenase, methemoglobin and glutathione levels. Hemoglobin electrophoresis was used to detect possible hemoglobin abnormalities. A battery of peripheral parameters was assayed to provide supplementary information and to assist in evaluation of overall physiological well-being. The specific serum, blood and urine parameters assayed have been discussed by Lubbers and Bianchine (*1*).

The numerical values obtained were collected and analyzed by utilizing the facilities of The Ohio State University Division of Computing Services for Medical Education and Research. Specially designed programs facilitated rapid clinical feedback. Any value for an individual subject which differed from the group mean by more than two standard deviations was noted. In addition, every individual value which fell outside normal laboratory ranges for that parameter was designated as abnormal. Chemical parameters for volunteers who exhibited abnormal values were subjected to careful scrutiny; the safety and the possibility of hypersensitivity to the disinfectant agents were evaluated for each of these individuals on a continuing basis throughout the study.

Statistical analyses utilized commercially available computer packages, specifically, the Biomedical Computer Programs (BMDP) and the Statistical Package for the Social Sciences (SPSS). Two-way analyses of variance with repeated measures utilized BMDP2V. BMDP1R was used to perform multiple linear regression analyses. For pairwise *t*-tests and simple *t*-tests, SPSS-*T*-test was employed.

Results

Qualitative

An important aspect of this study was the careful and continued medical observation of all subjects. The general clinical histories and physical examinations alone with subjective observations and qualitative laboratory tests throughout this study were accumulated in each subject's medical file. A careful

inspection of each of these medical files presented a review of the general clinical health of each subject.

The careful clinical evaluation of every subject in Phases I, II and III failed to reveal any clinically important impact upon the medical well-being of any subject as a result of disinfectant ingestion. Further, there was no apparent grouping of the minor subjective symptoms and objective signs noted throughout the study; the "colds," "lymphadenopathy," "sore throats" and "flu" problems noted episodically appear to be randomly dispersed among the treatment groups. All subjects remained negative with respect to the Coombs tests and the sickle cell tests during the investigation. Hemoglobin electrophoresis results indicated that, in Phase II, a small number of subjects yielded abnormal hemoglobin distributions but these individuals were found to be randomly distributed in both the treatment groups and in the control group. Examination of electrocardiograms revealed no abnormalities.

Vital signs (blood pressure, pulse rate, respiration rate and body temperature) were measured on a regular basis to provide immediate feedback to the monitoring physician on the acute physiological response of study participants to treatment. The statistical analysis of the vital signs was limited to the calculation of arithmetic group means and standard deviations from the mean. The compiled vital signs were examined for evidence of consistent response to treatment. No such evidence was found.

The subjective evaluations of palatability indicated that few subjects found the test substances to have an objectionable taste at levels up to 24 mg/l.

Quantitative

For the Phase I acute rising-dose tolerance study, a two-way analysis of variance with repeated measures was used to compare the treatment group values of each biochemical parameter to the corresponding values of the control group. The analysis of variance allowed distinctions to be made among the possible sources of variation. Differences between two groups that existed prior to treatment, parallel variations in quantitative chemical values due to laboratory drift and authentic treatment-related changes in physiological parameters could be distinguished. Three probabilities were calculated for each case: the group main effect (G), the time main effect (R), and group-time interaction (RG). The treatment groups and the corresponding biochemical parameters for which a strong probability of treatment-related change was computed (that is, RG $\leq$ 0.05) are listed in the first column of Table 3.

To assist in determining the clinical importance of the statistically significant group time interactions, the group, mean and standard deviations from the mean were examined for the pretreatment baseline assay and each posttreatment assay for each of the treatment groups. In all instances, the group mean values remain well within the established normal ranges.

On the basis of the small magnitude of change within the normal range and the duration of the study, it was concluded that the trends identified by the analysis of variance are unlikely to be of clinical importance. The possibility that the trends might become clinically important with increased exposure cannot be excluded.

Alternative statistical techniques were employed for Phase II. An omnibus testing technique was used initially. To test the hypothesis that the response of one or more of the groups was different to that of the rest of the groups, an analysis of variance with repeated measures was performed in which values for all six treatment groups were included. For the parameters urea nitrogen and mean corpuscular hemoglobin, RG-values < 0.05 were obtained. Supplementary tests were performed. Analyses of variance with repeated measures in which the values of each treatment group were compared to the corresponding values of the control group were chosen. The use of the analysis of variance in this manner is flawed by the common control group. However, the results of the analyses may be used with caution. The analysis of variance yielded statistically significant RG-values in the comparison of the group mean corpuscul ar hemoglobin values for the chlorite and the chlorate groups and of the group mean urea nitrogen values of chlorate and chlorine dioxide treatment groups to the corresponding control group values, as shown in Table 3.

No linear trends were detected by linear regression analysis of the chlorite group's mean corpuscular hemoglobin values, the chlorate group's urea nitrogen levels or the chlorite group's urea nitrogen values.

Mean corpuscular hemoglobin levels in the chlorate group yielded a probability of 0.01 upon linear regression analysis. The relative slope associated with the change during the 12-week treatment period was approximately 1% of the normal physiological range per week. We believe that no physiological importance may be attributed with confidence to the variation. However, it is impossible on the basis of this study to rule out the potential physiological significance of the trend. Further study is warranted.

The small number of subjects (three) in Phase III negated the value of many statistical procedures. Linear regression analyses were chosen. The third column of Table 3 lists the biochemical parameters for which a high probability of change with respect to time was calculated. The *p*-values computed by

Table 3. Biochemical parameters and treatment groups in which statistical analyses indicated a high probability of change which could be attributed to ingestion of disinfectant.

Test	Phase I[a]	Phase II[b]	Phase III[c]
Urea nitrogen (BUN)	Chlorite	Chlorate Chlorine dioxide	
Creatinine	Chlorite Chlorine		
BUN/creatinine Ratio	Chlorite		
Uric acid	Chlorine dioxide		
Calcium	Chlorine		
Gamma glutamyl transferase	Chlorine		
Total bilirubin	Chlorate		
Albumin/globulin ratio			Chlorite
Iron	Chlorate		
Methemoglobin	Chlorate		Chlorite
T-4 (RIA)			Chlorite
Free thyroxine index			Chlorite
Mean corpuscular hemoglobin		Chlorite Chlorate	
Mean corpuscular hemoglobin concentration			Chlorite
Lymphocytes	Chlorine		

[a]Two-way analysis of variance yielded group-time interactions (RG values) ≤ 0.05 in comparisons of treatment group values to those of the control group.

[b]Two-way analysis of variance yielded group-time interactions (RG-values) ≤ 0.05 in both the omnibus and treatment group-control group comparisons.

[c]Linear regression analysis indicated a strong probability of change with respect to time; p-values ≤ 0.05.

the linear regression analysis were less than 0.05 for four biochemical parameters. To gauge the relative magnitude of change, the percent change of the normal range per week was computed. These statistical analyses indicate a good probability that, for A/G ratio, T-4 (RIA), free thyroxine, mean corpuscular hemoglobin concentration, and methemoglobin values, a change with respect to time occurs during the 12-week treatment period. However, in the absence of a concurrent control group and taking into consideration the small group size and the possibility of laboratory drift, one must exercise caution in dealing with the results. We can say with confidence only that trends were indicated. We cannot say that these trends were of physiological origin nor can we attribute physiological consequence to them.

Discussion

Several researchers have addressed the physiological effects of oral ingestion of the oxidizing agents, chlorine dioxide, chlorite and chlorate. Musil et al. (*9*) associated oral chlorite ingestion with methemoglobin formation. In studies by Heffernan et al. (*7,8*), Abdel-Rahman et al. (*5*) and Couri et al. (*6*), hemolytic anemia and suppressed glutathione levels were observed in animals treated with chlorite. The oral administration of chlorate to laboratory animals has been shown to induce oxidative destruction of hemoglobin and methemoglobin formation (*10, 11*). The possibility of renal toxicity at high levels of chlorite ingestion was suggested by the increased kidney/body weight ratio reported by Heffernan et al. (*7*). Haller and Northgraves (*12*) and Fridlyand and Kagan (*13*) examined the chronic toxicity of orally consumed chlorine dioxide in rats; a slightly increased two-year mortality rate and a decreased rate of weight gain were observed. Oral administration of chlorite (*14–16*) to mice was shown to increase mean corpuscular volume, osmotic fragility, and glucose-6-phosphate dehydrogenase activity of erythrocytes; morphologic changes were reported. In the African Green monkey, chlorine dioxide adversely affected thyroid function; chlorite ingestion yielded transient changes in hemoglobin levels and red cell count (*17*). The maternal toxicity, embryonic toxicity and the teratogenic potential of concentrations of sodium chlorite was evaluated in rats (*18*).

Unfortunately, the information available on the impact of chlorine dioxide, chlorite, and chlorate ingestion in man is severely limited. Epidemiological studies (*19,20*) have failed to conclusively identify any significant exposure related effects. The clinical evaluation described in this report was an attempt to elucidate the effects of the chlorite, chlorine dioxide and chlorate in man under controlled clinical conditions.

During the course of the three-phase study, a massive volume of raw data was acquired. Routine urinalyses were performed and a meticulous exam-

ination of this body of information was made. No definitive finding of detrimental physiological impact was made in any of the three phases of this human investigation of the relative safety and tolerance of oral chlorine disinfectant ingestion. In several cases, statistically significant trends were associated with treatment; however, none of these trends were judged to have immediate physiological consequence. One cannot rule out the possibility that, over a longer treatment period, these trends might indeed achieve proportions of clinical importance. However, within the limits of the study, the relative safety of oral ingestion of chlorine dioxide and its metabolites, chlorite and chlorate, was demonstrated by the absence of detrimental physiological response.

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